IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Anne Eckart et al.**

Application No.: **10/088,139**

Examiner: **Hama, Joanne**

Filed: **December 17, 2002**

Art Unit: **1632**

Title: **Transgenic Animal Expressing a Multiple Mutated Form of Presenilin I**

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Commissioner for Patents
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APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. §41.37

Further to the Notice of Appeal dated June 18, 2008, the period for response having been extended in accordance with the attached Petition for Extension of Time, the following statements in support of the Appeal are submitted as detailed below.

APPELLANTS' BRIEF

(1) Real Party in Interest

The real party in interest is SANOFI-AVENTIS (by assignment to Aventis Pharmaceutical Inc. of December 17, 2002).

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 1-25 are pending. Claims 1-25 are rejected. Claims 1-25 are being appealed. All amendments filed have been entered or will be entered for purposes of appeal.

(4) Status of Amendments

Entered.

(5) Summary of Claimed Subject Matter

Independent claims 1 and 6 claim:

A transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue. [Claim 1].

A method for detecting compounds intended for the treatment of neurodegenerative diseases, comprising exposing said compounds to a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue. [Claim 6].

Specific support for claim 1 may be found in the specification as filed, for example, at page 33, lines 1-4 (Claim 1), page 4, lines 4 and 5 and 23-26; page 6, lines 2-6 and examples 1-5.

Specific support for claim 6 may be found in the specification, for example at page 33 (claims 1-6); page 3, lines 8-12; page 7, lines 15-19; and page 7, last three lines through page 8.

Independent claims 7 and 8 claim:

A cell extracted from a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue. [Claim 7]

A method for detecting compounds intended for the treatment of neurodegenerative diseases comprising exposing said compounds to a cell extracted from a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue. [Claim 8]

Specific support for claims 7 and 8 can be found in the specification, for example, at page 9, lines 1-5, Figure and at numerals 4 through 9 at page 17, line 13 through page 21, line 4. See also examples 2-8 (page 22, line 19 through page 29, line 20.

The specification as a whole provides additional more general support.

All rejected claims stand or fall together on the utility issue and the enablement issue as it is based on the utility rejection. Claim 21 is separately argued with respect to the breadth aspect of the 35 U.S.C. §112, first paragraph, rejection. Claims 2, 3, 9, 10, 13, 14, 17 and 18 are separately argued with respect to different breadth issues. Method claims 6, 8-20 and 22-25 are separately argued as opposed to claims 1-5, 7 and 21 (animal and cell claims) with respect to the manner of experimentation required in the context of the 35 U.S.C. §112, first paragraph rejection. Claim 3 and claim 21 are each separately argued with respect to specific mention of each claim in the Advisory Action wherein one aspect of the rejection was indicated not applicable to each respective claim.

(6) Grounds of Rejection for Review on Appeal

The issues for review on appeal are:

A) In a January 14, 2008 Final Rejection, claims 1-25 were rejected under 35 U.S.C. §101 as allegedly lacking utility. See Final Rejection pages 2-9.

B) In a January 14, 2008 Final Rejection, claims 1-25 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking utility and therefore allegedly lacking enablement. See Final Rejection pages 10-18.

(7) **Argument**

A) **The utility rejection under 35 U.S.C. §101 should be withdrawn at least in accordance with the argument of record and the following remarks.**

Applicants respectfully acknowledge the efforts of Examiner Hama in the July 15, 2008 Advisory Action. The under 35 U.S.C. §101 rejection is discussed at pages 2-10 of the Advisory Action. The comments of the Advisory Action will be addressed in the order they were presented.

The first aspect of rejection at pages 2 and 3 of the Advisory was:

> Applicant indicates that with regard to the Examiner indicating that the art teaches that Alzheimer's patients exhibit an increase in SOD and glutathione reductase activity and note that despite Examiner's assertion, not supported by reference to evidentiary data, the art also teaches the opposite. Applicant refers to publications and indicates that "falling levels of glutathione are associated with disease such as AIDS, respiratory diseases and infection, osteoarthritis, Alzheimer's and even aging itself" (Applicant's emphasis, Applicant's response, pages 5-6). In response, the Examiner has supported the issue that Alzheimer's patients exhibit an increase in SOD and glutathione reductase activity (Office Action, January 14, 2008, page 14, references to Delibas et al., 2002 and Lovell et al., 2000). With regard to Applicant referring to journal articles that indicate falling levels of glutathione being associated with disease including Alzheimer's disease, the Examiner cannot comment on the articles as they were not provided. With regard to Applicant indicating that falling levels of glutathione are related to various diseases, indicating that the claimed mice exhibit a decrease in SOD and glutathione reductase activity is not indicative that the mice are models of Alzheimer's disease. As indicated by the art indicated by Applicant, reduced SOD and glutathione reductase activity results in a number of diseases and is not necessarily indicative that the mice are models of Alzheimer's disease. In addition to this issue, as indicated by the Examiner, reduced levels of SOD and glutathione reductase are not necessarily indicative of Alzheimer's disease as Alzheimer's disease patients have been shown to exhibit increased SOD and glutathione reductase (see Delibas et al., 2002 and Lovell et al., 2000).

The primary basis for this rejection appears to be that the art is complex. While in some aspects of the disease under specific assays SOD and glutathione reductase may be said to be increased, in others they are decreased. Applicants respectfully observe that neither

SOD nor glutathione reductase is recited in claim language. The issue as framed in this basis of rejection appears to be not whether utility is credible, but whether there is unanimous agreement in the art. Applicants provided reference to the art in the June 18, 2008 reply, pages 4 and 5. Example 8 (pages 28 and 29) demonstrates SOD and glutathione reductase effects in the nervous tissue of the mouse model. Examples 3-5 (page 23, last 6 lines through page 25) demonstrate apoptotic phenomena of the multimutated transgenic mice. Further Example 6, page 26, lines 1-16, demonstrates , "in this model an impairment of a biochemical parameter (greatly affected in AD) which may underlie the hypersensivity to apoptosis."

Thus although the invention is acknowledged to be novel by the Examiner and thus utility is not plainly expressed in the art, the specification clearly asserts and demonstrates utility for the claimed mouse and methods using the mouse.

Applicants respectfully submit that this standard for utility finds no basis in law. At least this basis appears improper and would require that the rejection be reversed on these grounds.

A second basis of rejection can be found on pages 3 and 4 of the Advisory Action.

> Applicant indicates that Example 8 teaches that "(t)he deficiency in the mechanisms for protection against free radicals was also revealed in patients suffering from Alzheimer's disease, thus confirming the relevance of this animal model." Applicant requests an affidavit under 37 CFR 1.1 04(d)(2) that explains the Examiner's basis and rational to enable a formal response to this aspect of the rejection (Applicant's response, pages 6-7). **In response, it is not entirely clear what Applicant would like the Examiner to address.** [Applicants' emphasis.] With regard to 37 CFR 1.104 (d)(2):
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> > When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.
>
> if Applicant intends to indicate that the Examiner was depending on personal knowledge that If Applicant intends to mean that the Examiner's assertion that the deficiency in the mechanisms for protection against free radicals are not

confirmation of Alzheimer's disease, the Examiner has cited the teachings of Delibas et al., 2002 and Lovell et al., 2000.

Applicant's respectfully reply: The request for affidavit was with respect to the statement, made by the Examiner, that appeared to be incorrect.

The Examiner's assertion: "nothing in the art indicates that any of the characteristics exhibited by the mice (apoptotic lymphocytes and reduced SOD activity and reduced glutathione activity in the brain) are symptoms of Alzheimer's disease. It is noted at this point that the art teaches that Alzheimer's patients exhibit an increase in SOD and glutathione reductase activity." appeared to be plainly incorrect.

Applicants respectfully noted that despite the Examiner's assertion, was not supported by reference to evidentiary data, i.e., the art also teaches the opposite. Applicants provided a quote from the art found on the internet including supporting footnotes from the reference: "Scientists have proposed that elevated levels of one form of glutathione, the enzyme glutathione reductase, may serve as a predictor of longevity.[24,25] Falling levels of glutathione are associated with diseases such as AIDS, respiratory diseases and infection, osteoarthritis, **Alzheimer's,** and even aging itself.[26-33] Conversely, increased levels of glutathione are associated with improvements in these conditions."[1] The Examiner failed to present an

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[1] 24. Klapcinska B, Derejczyk J, Wieczorowska-Tobis K, et al. Antioxidant defense in centenarians (a preliminary study). Acta Biochim Pol. 2000;47(2):281-92.

25. Andersen HR, Jeune B, Nybo H, et al. Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. Age Ageing. 1998 Sep;27(5):643-8.

26. Micke P, Beeh KM, Buhl R. Effects of long-term supplementation with whey proteins on plasma glutathione levels of HIV-infected patients. Eur J Nutr. 2002 Feb;41(1):12-8.

27. Micke P, Beeh KM, Schlaak JF, Buhl R. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. Eur J Clin Invest. 2001 Feb;31(2):171-8.

28. Bishop C, Hudson VM, Hilton SC, Wilde C. A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. Chest. 2005 Jan;127(1):308-17.

29. Carlo MD, Jr., Loeser RF. Increased oxidative stress with aging reduces chondrocyte survival: correlation with intracellular glutathione levels. Arthritis Rheum. 2003 Dec;48(12):3419-30.

30. Cho CG, Kim HJ, Chung SW, et al. Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process. Exp Gerontol. 2003 May;38(5):539-48.

31. Junqueira VB, Barros SB, Chan SS, et al. Aging and oxidative stress. Mol Aspects Med. 2004 Feb;25(1-2):5-16.

affidavit at least to counter the statement "nothing in the art . . .." Applicants had observed that this statement was erroneous and therefore should not stand as a basis of rejection. This statement still appears to be erroneous and has not been supported by an affidavit as required by the rules. Reversal is therefore deemed proper.

The Advisory Action continued to ignore teachings in the art even after they were noted by Applicants:

> In response, as discussed in the Office Action, May 7, 2007, page 5, nothing in the art teaches a relationship between apoptotic lymphocytes and Alzheimer's disease. With regard to 37 CFR 1.104 (d)(2), the Examiner was not rejecting the instant claims based on personal knowledge. Rather, the Examiner has performed a search of the art and has not found any teaching between the relationship of apoptotic lymphocytes and Alzheimer's disease such that the claimed animals are a readily usable model. As for the phenotype of free radicals, the art, as discussed above, indicates that decreased levels of SOD and glutathione reductase are not indicative of Alzheimer's disease.

Paragraph bridging pages 5 and 6.

If not personal knowledge, then what can the statement that "nothing in the art teaches [something, anything]" be based on? Clearly the rejection is unsupported and improper.

The Office has not to date provided evidence that Applicants' observation that the Office Action was inaccurate should not force removal of this aspect of the rejection. Accordingly, this basis of rejection is improper and would require reversal of the rejection on these grounds.

Another aspect of the rejection appeared at page 6 of the Advisory Action. The Examiner's comments are provided below:

> Applicant indicates that the Office Action is clear in the in the intent to dismiss Applicant's utility and substitute a utility with a rational chosen by the Office, "while the mice described in the specification exhibit apoptotic lymphocytes, it is

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32. Lothian B, Grey V, Kimoff RJ, Lands LC. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. Chest. 2000 Mar;117(3):914-6.

33. Vina J, Lloret A, Orti R, Alonso D. Molecular bases of the treatment of Alzheimer's disease with antioxidants: prevention of oxidative stress. Mol Aspects Med. 2004 Feb;25(1-2):117-23.

> not clear what disease or disorder apoptotic lymphocytes is a symptom of. As such, the use of the claimed animals as a model of apoptotic lymphocytes is not readily apparent." Applicant has suggested a different utility and supported that utility with the specification and other evidence. It is not proper for the Office to select another utility as the utility upon which to base a rejection. Only one utility is required under 35 USC § 101 (Applicant's response, pages 7-8). In response, while Applicant asserts that the claimed animals are a model of disease and indicates the phenotypes the claimed animals exhibit, the Examiner does not find Applicant's assertion that the claimed animals are a model of disease to be persuasive. Applicant indicates that the claimed animals have apoptotic lymphocytes. However, the art does not teach a between mutated PS1, apoptotic lymphocytes, and Alzheimer's disease, such the claimed animals can be used.

Applicants stand by the assertion that Applicants are permitted to proffer utility [or if not utility is explicit, the art can provide utility]. Here, "the Examiner does not find Applicant's assertion that the claimed animals are a model of disease to be persuasive. Applicant indicates that the claimed animals have apoptotic lymphocytes. However, the art does not teach a relationship between mutated PS1, apoptotic lymphocytes, and Alzheimer's disease, such the claimed animals can be used."[2]

However, the Office Action further states:

> In response, while Applicant indicates that the claimed animals are a model of cell death in AD (wherein the specification teaches apoptotic lymphocytes, e.g. see page 10, legend of Figure 2), neither the art nor the specification teaches a relationship between mutant PS1, apoptotic lymphocytes, and AD such that the animal is a model of apoptotic lymphocytes seen in Alzheimer's patients.

See Advisory Action page 6, lines 8-13.

The Examiner here ignores the specification. AD is associated with presenilin. There appears to be no dispute on this matter. Lymphocytes are peripheral cells that may be apoptotic when endowed with multimutated presenilin (associated with AD). Accordingly peripheral tissues, such as lymphocytes, although they are not nervous tissue can exhibit some traits of AD and thus can serve as a model for screening, e.g., compounds or compositions,

[2] It appears that according to the Examiner one can not have both utility and novelty for an animal model. Unless the model is known in the art (and thus rejectable over prior art), then there can be no utility. This is not the law as following this logic, anything novel could be said to lack utility.

that may have effect in AD. Only a screen is asserted as utility. The claims do not rise to the level of claiming a cure or treatment for nervous disease possibly associated with presenilin.

The Advisory Action (page 6, line 15 through page 7, line 2) continues to maintain the proposition that utility requires lack of novelty in the following [Emphasis added.]:

> The claimed animals lack specific utility because the **art does not provide** guidance that apoptotic lymphocytes is a phenotype characteristic of Alzheimer's patients such that the claimed animals are a model of this aspect of Alzheimer's disease. The claimed animals also lack substantial utility **because the art does not teach** that apoptotic lymphocytes are a symptom of Alzheimer's disease such that the claimed animals can be used as a model of disease. While Applicant indicates a utility of the claimed animal in the specification, **the art at the time of filing does not support** an artisan finding the claimed animals as useful **because the art does not teach a relationship between PS1, apoptotic lymphocytes, and Alzheimer's disease**.

The Advisory Action continues to refer to a lack of novelty (absence in the art) as a requirement to possess utility. As stated previously this is an improper standard. The specification, i.e., the supporting written description, is one source that Applicants can rely upon for demonstrating utility. See e.g., MPEP 2107 II (B):

> (B) Review the claims and **the supporting written description** to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible:
>
> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

The Examiner has ignored the specification basing the alleged lack of utility on the lack of art teachings of utility. Ignoring the specification for utility and relying only on the art is not in keeping with established Office practice. Accordingly also on this basis the rejection is deemed improper and should be reversed.

At page 7, lines 7-11, the Advisory Action changes tact now asserting: "In response, while Applicant indicates this use of the apoptotic lymphocytes, this use is not specific and substantial. As discussed above, the art does not teach that apoptotic lymphocytes or

renewable tissues are a symptom of Alzheimer's disease such that the cells obtained from the claimed animals can be used as a model of disease." However, here an improper standard is also applied. Applicants did not propose an asserted utility that the apoptotic lymphocytes are a symptom of Alzheimer's disease. Curing apoptosis of lymphocytes is not the asserted utility. Rather use, e.g., of peripheral tissue such as lymphocytes, blood cells that contain DNA and have been shown to be sensitive to multimutated presenilin known to have an association with a nervous disease as a screening tool is asserted. The Examiner has continually tried to assert other utilities as a basis for rejection.

This is improper. The specification has asserted utility and provided experimental evidence in support. This evidence has not been challenged as incredible by the Examiner and thus is accepted. See, for example the Advisory Action at page 11, lines 12-14. Accepting this evidence provides the required evidence for utility. Thus this aspect of the rejection appears improper and should result in reversal of the rejection.

At page 8, lines 9-13, the Advisory Action appears to confuse utility with enablement. However, Applicants will address this aspect of the rejection presently [Emphasis added.]:

> while Applicant indicates that lymphocytes has some characteristics associated with neurodegenerative disease associated with oxidative stress, **this does not provide guidance for an artisan to use** the claimed invention because the art does not provide guidance between the relationship of PS1, apoptotic lymphocytes, and Alzheimer's disease.

The relationship discussed by the Examiner is not a requirement for use. For example: "exposing said compounds to a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue." (claim 6) can be performed without complete understanding of the relationship between "PS1, apoptotic lymphocytes, and Alzheimer's disease." The specification has shown a relationship in practice. See the examples discussed above. Additional guidance is unnecessary to establish utility (or enablement). Accordingly, on this aspect of the rejection proper procedure is not followed. Utility does not require guidance of a relationship. Association is adequate to demonstrate utility for the instant claims. Reversal of this rejection is respectfully requested.

At page 9, lines 1-9 and lines 12-17, the Examiner continues [Emphasis added.]:

> "'it cannot be extrapolated that apoptotic lymphocytes are models of Alzheimer's disease.' Applicant indicates that the statement is not fully supported by the simple premise that lymphocytic cells are not models of neuronal cells and requires an affadavit under 37 CFR 1.1 04(d)(2). In response, **the Examiner was not depending on personal knowledge**. Rather, **the Examiner** has looked through the art for guidance on other artisans using lymphocytes as models of neuronal conditions and **could not find any art**. As such, because there is no guidance for the relationship between PS1, apoptotic lymphocytes, and Alzheimer's disease, the instant invention lacks utility."
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> • • •
>
> while the specification asserts the utility of the claimed animals, the Examiner has not found these assertions to be persuasive that the claimed animals have a specific and substantial utility. **In searching the art, the art provides no guidance that there is a relationship between PS1, apoptotic lymphocytes, and Alzheimer's disease** such that the claimed animals are a model for any disease or disorder.

Once again the Examiner is relying on a lack of art (rather than teachings of the specification) to make a rejection based on lack of utility. The Examiner failed to find evidence in the art, e.g., using lymphocytes as models of neuronal conditions or using the claimed animals as a model. Once again, a finding of novelty appears as the basis of an assertion of lack of utility. As stated above, this is improper and argues once again for reversal of this rejection.

At page 10, lines 6 and 7, the Examiner once again substitutes a straw utility (a utility not relied upon by Applicants) to support this rejection: "While the claimed animals have a general utility in being used to treat apoptosis, this is not a specific use." Applicants do not claim that transgenic mice can be used as a treatment for Alzheimer's. Perhaps that may come in a later application, but is not presently claimed. However, Applicants cannot understand why treating apoptosis in a particular cell is de facto "not a specific use." Since this use is not relied upon to meet the utility requirement, no additional comment is deemed necessary.

In view of this argument and citation to evidence, the Board is respectfully requested to review and reverse the present 35 U.S.C. §101 rejection.

B) The lack of enablement rejection under 35 U.S.C. §112, first paragraph, should be withdrawn at least in accordance with the argument of record and the following remarks.

At page 10, lines 12-17, the Advisory Action presents the rejection under 35 U.S.C. §112, first paragraph as:

> Claims 1-25 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record, July 14, 2005, April 4, 2006, May 7,2007, January 14, 2008.

Accordingly, argument presented above demonstrating that the utility requirement has been met is relevant to this rejection and to the extent deemed necessary is incorporated herein by reference.

Although the examiner is on record as deeming the Application not incredible, at page 11, last 12 lines through page 12, line 5 the issue of novelty again appears [Emphasis added.]:

> The Examiner believes that the claimed animals exhibit the phenotypes as disclosed in the specification and that apoptosis is one contributing factor of Alzheimer's disease. However, as discussed above, the Examiner has looked in the art to determine what characteristics comprise Alzheimer's disease. **Nothing in the art teaches** that apoptotic lymphocytes are a characteristic of Alzheimer's disease. Similarly, with regard to the specification indicating that the claimed animals can be used to measure the symptom of apoptosis in renewable tissue, **the art does not teach** a relationship between apoptosis in renewable tissues and Alzheimer's disease such that the claimed animals can be used. With regard to indicating that the claimed animals exhibit a decrease in SOD and glutathione reductase activity, a characteristic seen in Alzheimer's patients, **the art teaches that Alzheimer's patients have also been shown** to exhibit an increase in SOD and glutathione reductase activity. With regard to using the claimed animals to studying a decrease in SOD and glutathione reductase activity and its relationship to apoptosis, this is not a specific and substantial use because any transgenic animal that exhibits apoptosis can generally be used to study apoptosis.

Again, the rejection appears based on an assertion of lack of novelty. Notably, undue experimentation is not a consideration here in supporting the rejection. The test for an

enablement rejection rests on the necessity for the skilled artisan to perform undue experimentation in order to practice the claimed invention.

Undue experimentation is in fact discussed in the Office Action at page 13, lines 7-11 [Emphasis added.]:

> because the art indicates that there is no relationship between PS1, apoptotic lymphocytes, and Alzheimer's disease. It would require **undue experimentation** for an artisan to identify the relationship between these three elements without any guidance from the art or specification.

The claims do not recite any requirement that any relationship be established. Accordingly, the manner of experimentation involved to establish such is not relevant to a 35 U.S.C. §112, first paragraph enablement rejection of the present claims. The rejection should therefore be reversed.

At page 14, lines 13 and 14, *Wands* is quoted: "However, experimentation needed to practice the invention must not be undue experimentation."

Key words here are, "to practice the invention." The claims define the invention. 35 U.S.C. §112, first paragraph does not in fact use the word "claim". Rather "invention" appears in the statute. However, since the statute at paragraph 2 requires claims "distinctly claiming . . . his invention", the invention must be taken as what is claimed, not what can be discerned from the disclosure in the specification. "Establishing" a relationship is not claimed and therefore experimentation to "establish" such is not an issue relevant to enablement of the present claims.

"Undue experimentation" is mentioned again in the following passage found at page 15, lines 4-14:

> In addition to the issue discussed above regarding it being undue experimentation for an artisan to determine what the relationship is between PS1, apoptotic lymphocytes, and a disease or disorder such that an artisan can use the claimed animals, the claims also encompass other issues of undue experimentation. This includes the art teaching that making transgenic animals with a predictable phenotype is not routine in the art (Office Actions, July 14, 2005, page 8 and May 7, 2007, pages 14-15, Hammer et al., 1990, Hammer et al., 1986, Auerbach, 2004 references). Applicant's claims encompass a wide variety of transgenic

> mammalian species and post-filing art indicates that it is not routine making different transgenic species in mammals with predictable phenotypes.

Applicants respectfully submit that "predictable phenotype" is not a proper assessment of the requirement for undue experimentation. Because some phenotypes are not transferable does not indicate that a transgenic animal (e.g., mammal) cannot be produced with only routine experimentation. The presenilin gene is known to exist across mammalian species. (Similar genes are native to invertebrate species such as *C. elegans*.) Finding the gene in a mammal thus would not raise a question of undue experimentation. The production of transgenics has been known in the art for years and accordingly can be characterized as routine can not properly be said to raise a question of undue experimentation. The issue is not "predictable phenotypes" in a general sense, rather the issue is making and using a mammal transgenic for and expressing a multimutated form of presenilin 1. See e.g., claim 1. No requirement for undue experimentation for this task has been alleged.

With respect to, "allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue" (claim 1), this recitation refers to the result of the creation of the transgenic mammal that is claimed. This is an expression of utility and follows from the expression of the multimutated form of presenilin 1. In the rare case that a peripheral tissue may not express presenilin 1 and as a result may not allow an apoptotic phenomenon to be detected in a renewable peripheral tissue, such event would be determinable with only routine, not undue experimentation.

Another aspect of this rejection rests on the observation:

> the claims broadly encompass any renewable tissue. However, the specification only teaches lymphocytes. The specification does not provide guidance for an artisan to practice the full breadth of the claimed invention as it is drawn to any renewable tissue. With regard to Applicant indicating that claim 3 is restricted to T lymphocytes and that the claim remains rejected (Applicant's response, page 14), it is noted that this aspect of the rejection does not apply to claim 3. However, claim 3 remains rejected for other reasons other than the breadth renewable tissues.

See page 16, last 9 lines.

Applicants respectfully submit that lymphocytes are renewable tissue and in fact are easily removed and assayed. This is one reason that biopsying lymphocytes is a preferred, e.g., specifically exemplified, embodiment. Biopsying other tissues is routine in the art, requiring no undue experimentation. Accordingly, although lymphocytes can be found in claims and in some examples, this does not indicate that undue experimentation is required for using another renewable peripheral tissue. The Office has not provided a rationale for the conclusion that substituting another tissue would require undue experimentation.

At page 17, lines 1-7 the Advisory Action harkens back to the "relationship issue:

> Applicant indicates on page 17, the Office Action discounts the evidence Page 17 in the specification that clearly supports association with Alzheimer's disease and again repeats an unsubstantiated claim that the phenotypes of Example 8 "are not indicative that the mice have any symptoms of Alzheimer's disease." In response, the Examiner addressed this issue on page 14 of the Office Action, January 14, 2008 and referred to publications by Delibas et al., 2002 and Lovell et al., 2000.

The reference to page 14 again speaks of the standard improperly applied and discussed above that anything novel cannot have utility established in the art.

> A search in the art has not indicated that there is a relationship presenilin, apoptotic lymphocytes and Alzheimer's disease.

January 14, 2008, Office Action, page 14, lines 5-7.

Thus this aspect of the enablement rejection has been discredited above and need not be readdressed here as no issue of undue experimentation appears to be included.

At page 17, lines 8-15, the Advisory Action states:

> With regard to the Office Action on page 17 indicating that "(a)s such, the use of the mice with regard to apoptotic lymphocytes to treat Alzheimer's disease is not readily apparent." Applicant indicates that they have not claimed use of the mice to treat Alzheimer's disease. Applicant requests an affidavit under 37 CFR 1.104 (d)(2) if the rejection is to be maintained. In response, the Examiner was not relying on personal knowledge. As discussed above, the Examiner was relying on the art for guidance on using transgenic animals that overexpress mutant presenilin.

The Examiner still has not explained why "use of the mice with regard to apoptotic lymphocytes to treat Alzheimer's disease" raises an issue with respect to enablement. Such is

not claimed. 35 U.S.C. §112, first paragraph does not in fact use the word "claim". Rather "invention" appears in the statute. However, since the statute at paragraph 2 requires claims "distinctly claiming . . . his invention", the invention is considered to be what is claimed, not what can be discerned from the disclosure in the specification. Accordingly, since treating Alzheimer's disease is not claimed, Applicant is not required to enable the process. The Examiner has asserted a claim construction not found in the text of the claim language, yet has refused to support this personal knowledge of claim construction with an affidavit. Reversal of this rejection is therefore deemed proper.

At page 17, 3 and 4 lines from the bottom, the Advisory Action states: "neither the art nor the specification provides other uses for the claimed animals." This is incorrect. For example the specification at page 3 discloses: "The present invention therefore resulted from the search for a new animal model representative of the neuropathology which makes it possible to measure the symptoms associated with AD, and in particular apoptosis, in peripheral tissues." And at page 7, lines 21-24: "this model allows, in comparison with known models, the detection of compounds which are particularly suitable for the treatment of AD, in particular as described in humans." Here, *inter alia,* are other uses clearly stated in the specification showing that the Advisory Action has overlooked pertinent portions of the specification which apparently has resulted in improper rejections. Applicants respectfully request reversal of the Examiner's rejections.

Separate Argument with respect to Claims 2, 3, 9, 10, 13, 14, 17 and 18

Claim 2 further limits claim 1 "in that it allows an apoptotic phenomenon to be detected in its lymphocytes." As a preliminary comment, Applicants make note that while claim 1 recites "peripheral tissue", the Advisory Action, e.g., throughout the utility rejection, is replete with mention of lymphocytes.

At page 16, lines 16-19, in the discussion of the enablement rejection, the Advisory Action observes:

> However, the specification only teaches lymphocytes. The specification does not provide guidance for an artisan to practice the full breadth of the claimed invention as it is drawn to any renewable tissue.

Thus the record acknowledges that lymphocytes are taught. Accordingly, reversal of this rejection is specifically requested based on the record at least with respect to the claims reciting lymphocytes, i.e., claims 2, 3, 9, 10, 13, 14, 17 and 18.

Separate Argument with respect to Claim 3

The Advisory Action at page 16, last two sentences states:

> With regard to Applicant indicating that claim 3 is restricted to T lymphocytes and that the claim remains rejected (Applicant's response, page 14), it is noted that this aspect of the rejection does not apply to claim 3. However, claim 3 remains rejected for other reasons other than the breadth renewable tissues.

Since it is noted that his rejection does not apply to claim 3, Applicants here separately argue the rejection and based on the statement in the Advisory Action urge reversal of the rejection or at least this aspect thereof.

Separate Argument with respect to Claims 10, 14 and 18

Claims 10, 14 and 18 also recite "T lymphocyte" or "T lymphocyte". The Advisory Action has specifically noted that at least one aspect of this rejection was not applicable to claim 3 based on the further limitation involving T lymphocytes. Applicants respectfully urge that the same reasoning applies to these claims and accordingly request reversal of at least this aspect of the enablement rejection for all of the claims reciting T lymphocyte(s).

Separate Argument with respect to Claims 1-5 and 21

Claims 1-5 and 21 feature transgenic mammals. The scope of enablement is thus distinguishable from claims reciting methods or cells from a mammal. The full scope of the transgenic mammal is the transgenic mammal itself. Making the mammals is taught by example at page 15 under numeral 2. Applicants have taught that the mammal can serve as a source of cells, e.g., T lymphocytes useful for screening for compounds that may lead to a cure or treatment for Alzheimer's Disease. This teaches "how to use", e.g., use the transgenic mammal as a source for cells, and thus satisfies the enablement requirement. . Applicants respectfully submit that reversal of the enablement rejection of claims 1-5 and 21 is proper.

Separate Argument with respect to Claim 7

Claim 7 features a cell extracted from a transgenic mammal of claim 1. Preparation of cells is exemplified in the specification, for example at page 17 under numeral 4. Use of these calls is exemplified, e.g., under numerals 5-9. Example 2, page 22, teaches successful use of these cells isolated from the mammals featured in claims 1-5 and 21. Accordingly, the how to use is also found in the specification. Applicants respectfully submit that reversal of the enablement rejection of claim 7 is proper.

Separate Argument with respect to Claims 6, 8-20 and 22-25

Claims 6, 8-20 and 22-25 are method claims. Claim 6 recites a method comprising "exposing said compounds to a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue". Utility of the method is taught by teaching how to perform the method thereby meeting the requirements of utility and enablement. See numerals 4 through 9 at page 17, line 13 through page 21, line 4. See also examples 2-8 (page 22, line 19 through page 29, line 20. These disclosures clearly demonstrate the actual performance of the method and useful results that may be achieved therefrom. The requirements under 35 U.S.C. §101 and under 35 U.S.C. §112 appear to be clearly met. Accordingly, Applicants respectfully submit that reversal of the enablement rejection of claim 7 is proper.

Separate Argument with respect to Claim 3

The Advisory Action at page 16, last two sentences states:

> With regard to Applicant indicating that claim 3 is restricted to T lymphocytes and that the claim remains rejected (Applicant's response, page 14), it is noted that this aspect of the rejection does not apply to claim 3. However, claim 3 remains rejected for other reasons other than the breadth renewable tissues.

Since it is noted that his rejection does not apply to claim 3, Applicants here separately argue the rejection and based on the statement in the Advisory Action urge reversal of the rejection or at least this aspect thereof.

Separate Argument with respect to Claim 21

Claim 21 further limits claim 1 by reciting "mouse". The Advisory Action, last three lines states:

Applicant indicates that claim 21 is included in the rejection and is drawn only to mouse and the rejection should not apply to this claim. In response, this aspect of the rejection does not apply to claim 21.

Since it is noted that his rejection does not apply to claim 3, Applicants here separately argue the rejection and based on the statement in the Advisory Action urge reversal of the rejection or at least this aspect thereof.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this submission to Deposit Account 18-1982.

Respectfully submitted,

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(8) Claims Appendix

The appealed claims are:

1. A transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue.

2. The transgenic animal according to claim 1, characterized in that it allows an apoptotic phenomenon to be detected in its lymphocytes.

3. The transgenic animal according to claim 2, characterized in that it allows an apoptotic phenomenon to be detected in its T lymphocytes.

4. The transgenic animal according to claim 1, characterized in that the mutations in the PS1 gene are at least three mutations selected from the group consisting of M146L, H163R, A246E, L286V, C410Y, I143T, L235P, P264L, P267S, E317G, G384A, L392V, A426P and P436S.

5. The animal according to claim 4, characterized in that the mutations are M146L, H163R, A246E, L286V, C410Y, combined with each other.

6. A method for detecting compounds intended for the treatment of neurodegenerative diseases, comprising exposing said compounds to a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue.

7. A cell extracted from a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue.

8. A method for detecting compounds intended for the treatment of neurodegenerative diseases comprising exposing said compounds to a cell extracted from a transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue.

9. The method according to claim 6, characterized in that an apoptotic phenomenon is detected in lymphocytes.

10. The method according to claim 9, wherein the lymphocytes are T lymphocytes.

11. The method according to claim 6, characterized in that the mutations in the PS1 gene are at least three mutations selected from the group consisting of M146L, H163R, A246E, L286V, C410Y, I143T, L235P, P264L, P267S, E317G, G384A, L392V, A426P and P436S.

12. The method according to claim 11, wherein the mutations are M146L, H163R, A246E, L286V, C410Y, combined with each other.

13. The cell according to claim 7 which is a lymphocyte.

14. The cell according to claim 13 wherein the lymphocyte is a T lymphocyte.

15. The cell according to claim 7 having at least three mutations in the PS1 gene selected from the group consisting of M146L, H163R, A246E, L286V, C410Y, I143T, L235P, P264L, P267S, E317G, G384A, L392V, A426P and P436S.

16. The cell according to claim 15 wherein the mutations are M146L, H163R, A246E, L286V, C410Y, combined with each other.

17. The method according to claim 8, characterized in that an apoptotic phenomenon is detected in lymphocytes.

18. The method according to claim 17, wherein the lymphocytes are T lymphocytes.

19. The method according to claim 8, characterized in that the mutations in the PS1 gene are at least three mutations selected from the group consisting of M146L, H163R, A246E, L286V, C410Y, I143T, L235P, P264L, P267S, E317G, G384A, L392V, A426P and P436S.

20. The method according to claim 19, wherein the mutations are M146L, H163R, A246E, L286V, C410Y, combined with each other.

21. The animal according to claim 1 which is a mouse.

22. The method according to claim 6 wherein the neurodegenerative disease includes impairments in mechanisms for protection against free radicals.

23. The method according to claim 22 wherein the neurodegenerative disease is Alzheimer's disease.

24. The method according to claim 8 wherein the neurodegenerative disease includes impairments in mechanisms for protection against free radicals.

25. The method according to claim 24 wherein the neurodegenerative disease is Alzheimer's disease.

(9) Evidence Appendix

None

(10) Related Proceedings Appendix

None.